

Applying Pharmacokinetic/Pharmacodynamic Principles in Critically Ill Patients: Optimizing Efficacy and Reducing Resistance Development

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Abstract

The recent surge in multidrug-resistant pathogens combined with the diminishing antibiotic pipeline has created a growing need to optimize the use of our existing antibiotic armamentarium, particularly in the management of intensive care unit (ICU) patients. Optimal and timely pharmacokinetic/pharmacodynamic (PK/PD) target attainment has been associated with an increased likelihood of clinical and microbiological success in critically ill patients. Emerging data, mostly from in vitro and in vivo studies, suggest that optimization of antibiotic therapy should not only aim to maximize clinical outcomes but also to include the suppression of resistance. The development of antibiotic dosing regimens that adheres to the PK/PD principles may prolong the clinical lifespan of our existing antibiotics by minimizing the emergence of resistance. This article summarizes the relevance of PK/PD characteristics of different antibiotic classes on the development of antibiotic resistance. On the basis of the available data, we propose dosing recommendations that can be adopted in the clinical setting, to maximize therapeutic success and limit the emergence of resistance in the ICU.

Keywords

- antibiotic
- resistance
- pharmacodynamics
- pharmacokinetics
- antibiotic dosing

Severe infections leading to severe sepsis and septic shock are prominent causes of morbidity and mortality in critically ill patients. In a large multicenter point prevalence study involving 1,265 intensive care units (ICUs) across 75 countries, 51% of ICU patients were classified as infected on the day of study with a mortality rate of 25.3%.¹ Data from a large European ICU study has further corroborated the diagnosis of severe sepsis as a global healthcare crisis, whereby the condition accounted for 26.7% of ICU admissions.² In this study, the corresponding mortality in patients with severe sepsis and septic shock was of concern, with rates of 32.2 and

54.1%, respectively.² Despite an emerging trend for improved survival over recent years,^{3–5} the mortality rate in this patient cohort remains unacceptably high worldwide.⁶ In the context of the financial burden incurred, the United States is currently spending between \$121 and \$263 billion annually on critically ill patients, which represents more than 8% of the country's total healthcare expenditure.⁷

To address these persisting poor patient outcomes, significant amounts of research have been directed toward optimizing the provision of care for the critically ill patient. Indeed, improving antibiotic therapy is a core focus of

treatment of infection-driven pathologies such as sepsis. There is strong evidence to suggest that optimal antibiotic therapy may have a greater impact on patients' survival when compared with novel treatment strategies such as the use of activated protein C,⁸ antithrombin III,⁹ and intensive insulin therapy in these patients.^{10–13} However, the process of optimizing antibiotic therapy can be a daunting challenge in the ICU for a variety of reasons. Extreme physiological derangements that can occur from either pharmacological interventions or the natural course of critical illness may alter antibiotic concentrations and consequently reduce antibiotic exposure in critically ill patients.¹⁴ In addition, pathogens that are usually isolated in the ICU differ from the general wards, as they are commonly less susceptible to common antibiotics.^{15,16} Indeed, antibiotic dosing that does not account for these features is likely to lead to suboptimal antibiotic exposure and therapeutic failures. In addition, suboptimal antibiotic exposure is also highly implicated as a contributing factor to the escalation of antibiotic resistance. Resistance to antibiotics certainly is considered a global healthcare crisis which currently threatens the advances of modern medicine.¹⁷

The recent surge in multidrug-resistant (MDR) pathogens combined with the diminishing antibiotic pipeline has created a growing need to optimize the use of the existing antibiotic armamentarium, particularly in the ICU. Although critically ill patients constitute fewer than 10% of all hospital admissions, their antibiotic consumption is 10 times greater compared with patients in all other wards.^{18–20} The rampant antibiotic use (or misuse) has therefore, in part, contributed to the alarming increase in the MDR pathogens such as the extended spectrum β -lactamases and carbapenemase-producing gram-negative pathogens. Notably, gram-negative pathogens such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, as well as members of the Enterobacteriaceae family such as *Escherichia coli* and *Klebsiella pneumoniae*, which were previously considered relatively innocuous, have impressively out-manuevered our current antibiotics. Previously simple infections have become increasingly difficult to treat over a short period of time.²¹ Moreover, infections caused by these pathogens frequently result in poor clinical outcomes, including higher mortality and prolonged hospitalisation.^{22–24} The healthcare community concerns are legitimate, as the emergence of resistance is likely to far outpace the rate of development of new antibiotics. In light of these grim prospects, clinicians are currently forced to reintroduce older antibiotics as treatment options (e.g., colistin and fosfomycin) and vigorously search for new strategies that can optimize the use of our presently available antibiotics.

The aim of this article is to describe the relevance of pharmacokinetic (PK) exposure and pharmacodynamic (PD) characteristics of different antibiotic classes on the development of antibiotic resistance. We will discuss the relevant antibiotic resistance descriptors and review how target drug exposures differ between predicting treatment success and suppressing resistance development. On the basis of these current data, we will also suggest dosing strategies that ultimately exploit antibiotic pharmacodynamics which in-

crease the likelihood of treatment success as well as minimize the emergence of resistance.

Applied Clinical Pharmacology of Antibiotics

Pharmacology is the science of drugs including the study of drug actions. Two principle areas of pharmacology are PK and PD. Traditionally, antibiotic dosing and administration were only optimized, in accordance with the PK/PD principles, for clinical efficacy (i.e., clinical and microbiological cure) with an associated collateral damage being the selection of resistant pathogens. Emerging data are suggesting that the PD-based dosing approach should not only aim to maximize clinical outcomes but also to include the suppression of resistance. Indeed, the application of PK/PD principles has been shown to minimize the risk of emergence of resistance by avoiding ineffective antibiotic exposure, which consequently exerts a selective pressure to pathogens, rather than to eradicate them.²⁵ This selective pressure causes the elimination of highly susceptible, but not the more resistant colonies, leading to future colonization and potential infection with poorly susceptible pathogens.

Pharmacokinetic Considerations

PK refers to the study of concentration changes of a drug over a given time period. This branch of pharmacology describes the rates and processes from absorption to distribution of drugs to elimination mechanism via metabolism or excretion. Some of the examples of important PK parameters are (1) volume of distribution (V_d), (2) clearance (CL), (3) maximum drug concentration over a dosing interval (C_{max}), (4) minimum drug concentration during a dosing interval (C_{min}), and (5) area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}). Among these however, alterations in the primary PK parameters, namely V_d and CL, are probably the most influential in determining altered antibiotic dosing and exposure. Changes in antibiotic V_d and CL have been commonly observed in critically ill patients and the relevance of the two phenomena in influencing effective antibiotic exposure has been reviewed in detail elsewhere.²⁶

Pharmacodynamic Considerations

PD describes the relationship between PK exposure and pharmacological effect. For antibiotics, PD relates the antibiotic concentration to the ability of an antibiotic to kill or inhibit the growth of a pathogen. In general, this relationship is often described by linking the concentration of an antibiotic with the corresponding minimum inhibitory concentration (MIC) of the offending pathogen. For an antibiotic, it is the free or unbound concentration that is responsible for the antibiotic activity.²⁷ Numerous studies have demonstrated that different antibiotics have different PD properties and can be readily categorized as the following: (1) the duration of time that free drug concentration remains above the MIC during a dosing interval ($fT_{>MIC}$), (2) the ratio of C_{max} to MIC, and (3) the ratio of AUC_{0-24} to MIC. These fundamental PK/PD indices for antibiotics' activity are further illustrated in ►Fig. 1. It should be noted that the AUC/MIC was never

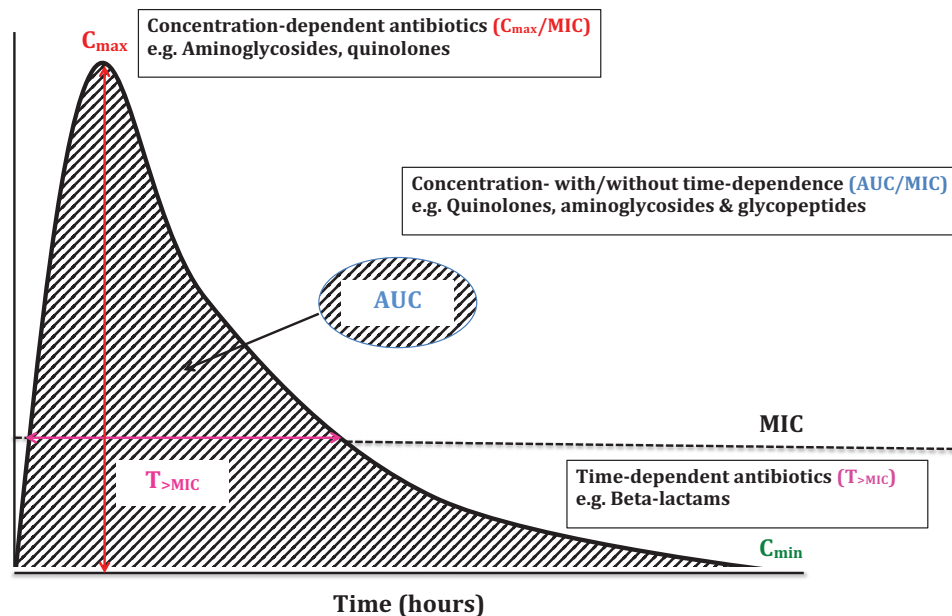


Fig. 1 The graphical illustration of fundamental pharmacokinetic and pharmacodynamic parameters of antibiotics on a hypothetical concentration–time curve. AUC, area under the concentration–time curve; C_{\max} , maximum drug concentration; C_{\min} , minimum drug concentration; MIC, minimum inhibitory concentration; $T_{>MIC}$, duration of time that drug concentration remains above MIC.

considered in earlier studies, and that many data retrieved from older literature established only the relationship between C_{\max}/MIC and effect parameter. From a theoretical point of view, most of the antibiotics should show a relationship with AUC and effect rather than C_{\max} .

Based on the PK/PD indices, antibiotics can be classified into three categories that, by and large reflect their modes of bacterial killing.^{28–30} The first category includes antibiotics where the difference between the maximum effect and minimum effect is relatively large, and increasing concentrations result in progressively increased killing. Therefore, these are also sometimes called concentration-dependent antibiotics, and include aminoglycosides and quinolones. For these antimicrobials, AUC/MIC describes their antibiotic activity best, and, mainly because AUC/MIC is closely correlated to C_{\max}/MIC , C_{\max}/MIC as well.^{31,32} On the other hand, time-dependent antibiotics' activity, such as the β -lactams, is strongly correlated with $fT_{>MIC}$ and as such, prolonging the duration of effective drug exposure should be the priority when this antibiotic class is used.^{33,34} However, some antibiotics such as the glycopeptides are more complex where they are found to display both concentration- and time-dependent kill characteristics.³⁴ For these antibiotics, the ratio of AUC_{0-24}/MIC describes their antibiotic activity best and higher thresholds are closely related to successful clinical outcome.³⁵

Pharmacokinetic/Pharmacodynamic Considerations and the Resistance Descriptors

Most of the earlier research on optimizing antibiotic dosing was focused only on maximizing clinical and microbiological

cure and not on minimization of the emergence of antibiotic resistance. To date, most of the data describing PK/PD and its association with antibiotic resistance comes from preclinical, albeit advanced, PK/PD infection models. However, the antibiotic exposure required for clinical efficacy and resistance suppression is markedly different. For instance, the antibiotic exposure–response relationship for clinical efficacy is monotonic or can also be described as a sigmoidal relationship in which no measurable antibiotic effect is expected at lower drug exposures while larger exposures are expected to augment the bactericidal effect up to a certain threshold. In contrast, the relationship between antibiotic exposure and the selection of resistant mutants is markedly non-monotonic and has the shape of an inverted “u,” where resistant mutants are amplified with initial antibiotic exposure and then slowly decline with increasing exposure up to an optimal threshold that ultimately prevents resistance amplifications.^{36–39} The inverted u-shape seems to follow a log normal distribution.⁴⁰ In addition, Jumbe et al⁴⁰ found that an AUC_{0-24}/MIC of ≥ 110 for levofloxacin, which was twice that was necessary for optimal bactericidal effect, was required to suppress drug-resistant population of *P. aeruginosa* in a mouse thigh infection model.⁴¹ This information, among other similar observations, has indicated that the magnitude of the PK/PD indices for resistance suppression is generally different and higher than the thresholds required for clinical success.^{37,42–44} Therefore, antibiotic dosing that only aims to optimize clinical efficacy may potentially amplify resistance formation by selecting mutant bacterial strains with reduced drug susceptibility. With enhanced knowledge on antibiotic PK/PD over recent years, important hypotheses and concepts, such as the mutant selection window (MSW) and mutant prevention concentrations (MPCs), have been proposed to provide

potential explanations as to how suboptimal antibiotic exposure may amplify the selection of resistant bacterial strains. In addition, the dynamics of bacterial populations under various dosing regimens can be described using mixture models, where changes in susceptible and resistant subpopulations in relation to drug concentrations are quantified.^{38,41,42,45,46}

Mutant Selection Window

The term “selective window” (SW), which was first coined by Baquero,^{47,48} refers to a critical range of antibiotic concentrations in which drug-resistant bacterial mutants could be selectively enriched and amplified when exposed to concentrations in this zone. Subsequent *in vitro* studies, utilizing mycobacteria treated with quinolones, were able to define the boundaries for the critical zone of antibiotic concentrations and this concept was later renamed as the MSW.^{49–51} Studies that attempted to describe MSW further suggested that these concentration zones are those between the MIC of the susceptible pathogens and that of the least susceptible mutants. ▶Fig. 2 illustrates the concept of MSW and its relevance in the development of resistant mutants. In addition to this, the formation of the resistant mutants was observed to be most intense in the bottom portion as opposed to the upper portion of the selection window.⁵² The existence of such “dangerous” concentration zones was further corroborated by several *in vitro*^{39,53–55} and *in vivo* experimental studies.^{56–59}

The MSW hypothesis is potentially important, as contemporary antibiotic dosing tends to produce drug concentrations within the critical zone where they selectively amplify the growth of resistant mutants. Essentially, the higher the percentage of time (*t*) spent by an antibiotic within the MSW (*t*MSW), the greater the opportunity for resistant mutants to be selected and amplified. Furthermore, the continuous and prolonged “careless” practice of “dosing to only cure” in the ICU eventually leads to the resistant mutants being the dominant bacterial population and it is only at this point that surveillance studies would be alerted to the emergent resistant isolates. The MSW has been defined for many of the quinolones and some of the β -lactams against various microorganisms.^{60–62} Nevertheless, this concept is currently considered as a relatively new idea and has not been investigated in many infective pathologies, nor its relevance at the site of infection. Hence, its clinical relevance in optimizing antibiotic dosing to avoid the MSW remains unclear and warrants further investigation.

Mutant Prevention Concentration

The concept of MPC, which was derived from the MSW hypothesis, refers to the antibiotic concentration that corresponds to the MIC of the least susceptible mutants in a colony.^{49,51} While MIC refers to the lower boundary, the MPC essentially represents the upper boundary of concentrations in the MSW in which the enrichment of resistant

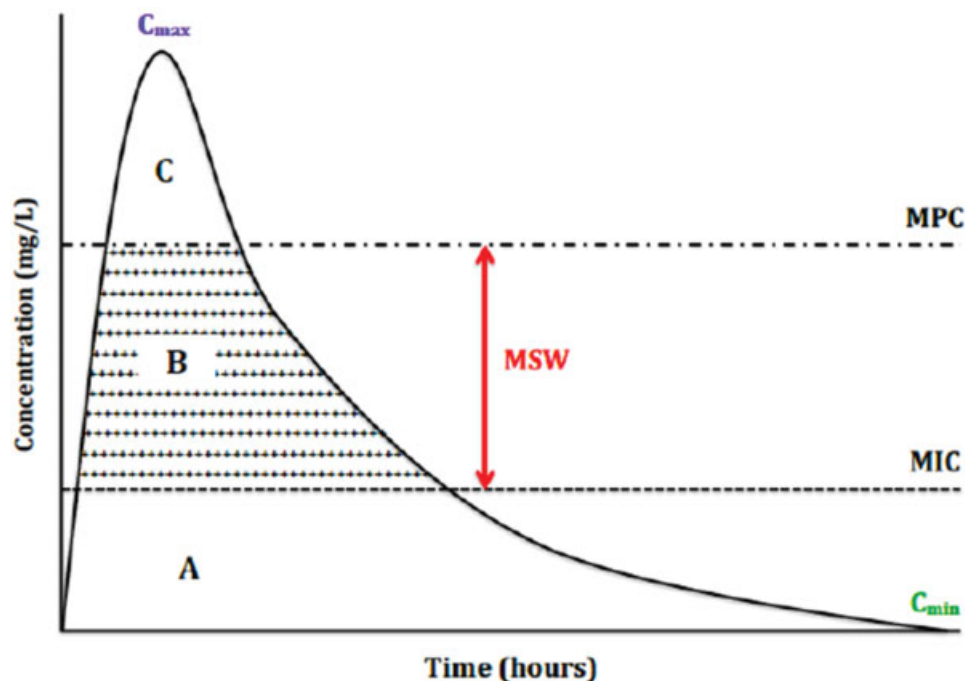


Fig. 2 Graphical illustration of the mutant selection window and mutant prevention concentration on a hypothetical concentration–time curve. The MSW describes the range of antibiotic concentrations where resistant mutants may be selectively amplified and these concentration zones are those between the MIC of the susceptible pathogens and that of the least susceptible mutants, i.e., MPC. In area (A), which is below the MIC, no resistant mutants are expected to grow, as there is no selective pressure in this area. In area (C), which is above the MPC, the growth of resistant mutants is severely restricted and highly unlikely as the exposure in the area is able to suppress the growth of the least susceptible pathogens. On the contrary, the selection of resistant mutants would be most intense in area (B) which is also known as MSW. Conversely, the longer the time spent by an antibiotic in this concentration zone, the greater the opportunity for resistant mutants to be selected and amplified. C_{max} , maximum drug concentration; C_{min} , minimum drug concentration; MIC, minimum inhibitory concentration; MPC, mutant prevention concentration; MSW, mutant selection window.

mutants are expected to be severely hindered. Conversely, antibiotic dosing that aims to achieve concentrations higher than the MPC, as opposed to MIC, theoretically provides both an optimal bactericidal effect and resistance suppression. Furthermore, the ratio of AUC_{0-24} to MPC (AUC_{0-24}/MPC) as opposed to AUC_{0-24}/MIC is also suggested as a predictor of the development of resistance in several in vitro and in vivo evaluations as MIC quantifications generally ignore mutant subpopulations.^{36,60,63,64} The argument has been mostly tested in in vitro studies for quinolones where the mutant-restrictive thresholds of AUC_{0-24}/MPC were approximately one-third of those AUC_{0-24}/MIC values.^{39,65}

The MPC has been described mostly for quinolones, although data for other classes of antibiotics are emerging.^{60,66,67} Quantifying MPC thresholds for individual antibiotics should be one of the priorities in the development of dosing guidelines especially earlier in the process of evaluation and screening of new compounds. Although the concept seems appealing, the application, however, is not straightforward, as the doses needed to achieve the MPC are usually higher than those for curing patients and exceed those that are registered for those antibiotics. There are also examples where these concentrations are unattainable for some antibiotic-pathogen combination.^{50,67} In addition, a trade-off between an increased risk of adverse effects with minimizing antibiotic resistance is a difficult consideration in clinical practice. In such cases, combining two or three antibiotics with overlapping PD properties may be warranted.

Application of Experimental Mixture Models

Mixture models examine resistance development by describing the population dynamics of antibiotic-susceptible and -resistant bacteria during the course of treatment. Susceptible and resistant subpopulations respond differently to different antibiotic concentrations.

In a murine thigh infection model, Jumbe et al investigated the impact of bacterial inoculum on the required levofloxacin exposure for the eradication of the total *P. aeruginosa* population.⁴¹ The mice were inoculated with either 10^7 or 10^8 bacteria per thigh and levofloxacin was initiated after 2 hours. The investigators demonstrated that the exposure intensity which is required for maximal levofloxacin activity increases (by two- to fivefold) as the size of the inoculum increases by 1 log. This phenomenon occurs as a larger bacterial challenge constitutes larger population of resistant mutants, which are less susceptible to antibiotic therapy. The investigators also employed a complex mathematical model to analyze their findings and simultaneously calculate an exposure that would amplify resistant population and restrict the enrichment of the population. A free AUC/MIC ratio of 110 and 36 was predicted to prevent and amplify resistant *P. aeruginosa* mutants in the study, respectively.

Specific Antibiotic Classes

This section discusses individual antibiotic classes and their pharmacodynamic characteristics, which influence antibiotic activity and the prevention of resistance. The relevant PD

indices that have been shown to correlate with both outcomes are presented in ►Table 1.

Quinolones

Quinolones are mostly lipophilic antibiotics and display largely concentration-dependent kill characteristics but with some time-dependent effects. Previous in vitro studies have shown that the achievement of a C_{max}/MIC ratio of at least 8 to 12 is important for optimal bactericidal activity.^{68,69} Given the half-life of most quinolones, this corresponds to AUC_{0-24}/MIC values that correlate to efficacy. More important, however, is that the index has also been associated with the reduction of resistant mutants in several experimental studies.⁷⁰⁻⁷²

Several studies found that the ratio of AUC_{0-24}/MIC is important for its bactericidal effect, as an even more significant index as compared with the C_{max}/MIC ratio, and a ratio of ≥ 125 and ≥ 30 has been advocated for clinical success in the treatment of gram-negative and -positive infections, respectively.^{71,73-77} In the context of antibiotic resistance, an inverse relationship has been described between this index and the probability of developing resistance.⁷⁸ Accordingly, quinolone dosing regimens that ensure higher ratios of AUC_{0-24}/MIC are currently recommended to maximize bactericidal exposure as well as minimizing the development of resistance.^{38,41,78} Several investigators have further elucidated the critical AUC_{0-24}/MIC thresholds as being between >100 and 200 to suppress the formation of resistant mutants when these antibiotics are used for gram-negative infections.^{41,78,79} However, owing to intrinsic differences between various quinolones in selecting resistant strains, the suggested AUC_{0-24}/MIC ratio for resistance suppression may vary between individual agents.^{71,80}

The AUC_{0-24}/MPC index is also being investigated and the advantages over AUC_{0-24}/MIC in the prediction of resistance development have been documented in several in vitro studies.^{60,63,64} To date, this remains a controversial argument as most authors found that both indices were similar in their predictive potentials of resistance development.^{57,81} Nevertheless, higher ratios of AUC_{0-24}/MPC are associated with minimizing the emergence of resistance.

Recently, increasing interest and efforts have been focused on the application of MSW concept in the evaluation of quinolones dosing regimens. Based on the current data, $tMSW$ of $\leq 30\%$ should restrict mutant amplification and the index has been studied in several in vitro^{55,82} and in vivo studies.^{57,61} Khachman et al further extended this concept into clinical practice by investigating the appropriateness of the currently recommended ciprofloxacin dosing in 102 critically ill patients.⁸³ Using Monte Carlo simulations, the probability of target attainment (i.e., $\leq 20\%$ $tMSW$) for the currently recommended ciprofloxacin dosing regimens (i.e., 800 mg or 1,200 mg/daily) was less than 50% and when higher doses such as 2,400 mg/daily were used, only minor improvements were observed, that is, probability of target attainment of 61%. More importantly, the risk of selecting resistant *A. baumannii* and *P. aeruginosa* strains were extremely high with the recommended regimens, thus challenging their appropriateness in critically ill patients. As it

Table 1 Optimal pharmacokinetic/pharmacodynamic indices for antibiotic activity and the magnitudes associated with maximal therapeutic outcomes and resistance suppression^a

Antibiotic class	Optimal PK/PD index	PK/PD magnitude for bacterial killing ^b	PK/PD magnitude for clinical efficacy ^c	Optimal PK/PD index for resistance suppression	PK/PD magnitude for resistance suppression ^d
Aminoglycosides	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 80–160 ^{86,88,90}	AUC ₀₋₂₄ /MIC: 50–100 ⁸⁹	C _{max} /MIC	C _{max} /MIC ≥ 20 ⁹⁴
	C _{max} /MIC	–	C _{max} /MIC ≥ 8 ^{31,66,87}		C _{max} /MIC ≥ 30 ⁹⁴
Penicillins	T _{>MIC}	≥40–50% T _{>MIC} ³⁴	≥40–50% T _{>MIC}	T _{>MIC}	≥40–50% T _{>MIC} ⁶²
Cephalosporins	T _{>MIC}	≥60–70% T _{>MIC} ³⁴	≥45–100% T _{>MIC} ^{32,99,102,103}	tMSW	≤40% tMSW ¹¹²
Carbapenems	T _{>MIC}	≥40% T _{>MIC} ³⁴	≥50–75% T _{>MIC} ^{105,107}	T _{>MIC}	≥40% T _{>MIC} ¹¹⁶
				tMSW	≤45% tMSW ¹¹⁷
Quinolones	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 30–200 ^{29,76,77}	AUC ₀₋₂₄ /MIC: 35–250 ^{71,73–75}	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 100–200 ^{38,41}
	C _{max} /MIC	C _{max} /MIC ≥ 8 ^{68,69,72}	C _{max} /MIC ≥ 8 ⁸⁸	C _{max} /MIC	C _{max} /MIC ≥ 4 ⁷⁰
				AUC ₀₋₂₄ /MPC	AUC ₀₋₂₄ /MPC ≥ 22 ⁶⁰
				tMSW	≤30% tMSW ^{53,55,59,82}
Vancomycin	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 86–460 ³⁴	AUC ₀₋₂₄ /MIC: 400–600 ^{34,128}	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 200 ⁵³
Linezolid	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 50–80 ¹³⁶	AUC ₀₋₂₄ /MIC ≥ 80 ¹³⁷		
	T _{>MIC}	≥40% T _{>MIC} ^{136,138}	≥85% T _{>MIC} ¹³⁷		
Daptomycin ^e	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 388–537 ¹⁴⁹	–	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 200 ⁵³
	C _{max} /MIC	C _{max} /MIC: 59–94 ¹⁴⁹	–		
Fosfomycin	Unknown	–	–	–	–
Colistin	AUC ₀₋₂₄ /MIC	AUC ₀₋₂₄ /MIC: 50–65 ^{175,176}	–	–	–

Abbreviations: AUC₀₋₂₄/MIC, ratio of area under the concentration–time curve during a 24-hour period to minimum inhibitory concentration; AUC₀₋₂₄/MPC, ratio of area under the concentration–time curve during a 24-hour period to the concentration that prevents mutation; C_{max}/MIC, ratio of maximum drug concentration to minimum inhibitory concentration; T_{>MIC}, duration of time that drug concentration remains above the minimum inhibitory concentration during a dosing interval; tMSW, percentage of time spent by an antibiotic within the mutant selection window.

^aAll values refer to the nonprotein bound, free fraction except when indicated otherwise.

^bData have been summarized from in vivo animal studies and may utilize different infection models employing different bacteria. Where the index is reported as a range, specific data for the contributing indices, which may have been derived from different studies, can be found in the associated references. The data also reflect the 2-log kill and in some cases 1-log kill which may or may not coincide with maximum kill.

^cData have been summarized from clinical studies and may recruit different patient population. Where the index is reported as a range, specific data for the contributing indices, which may represent PK/PD thresholds for clinical or microbiological cure, can be found in the associated references.

^dData have been summarized from preclinical studies, which may include in vitro and in vivo experimental infection models employing different bacteria. Specific data for the contributing indices can be found in the associated references.

^eValues reported here refer to total drug concentration.

stands, a quinolone dosing regimen that maximizes the AUC₀₋₂₄/MIC ratio should be considered in critically ill patients and by citing ciprofloxacin as an example; the objective may be achieved with a 400 mg 8-hour or 600 mg 12-hour regimen. When treating pathogens with high MICs, dose escalation should be considered while being observant of possible occurrence of dose-related adverse effects.

Aminoglycosides

Aminoglycosides are hydrophilic in nature and they demonstrate concentration-dependent kill characteristics.^{31,84} Although previous studies have mainly suggested that achieving a high C_{max}/MIC ratio predicts optimal outcome,^{32,85–88} Craig argued that the ratio of AUC₀₋₂₄/MIC would be more appropriate in describing the antibiotic's

activity.³⁴ In the 1980s, Moore et al³² suggested that an aminoglycoside dose that provided a C_{\max}/MIC ratio of 8 to 10 was associated with a higher probability of clinical success against gram-negative infections. However, the investigators chose the index due to their sparse PK sampling times and consequently, $\text{AUC}_{0-24}/\text{MIC}$ ratio was not considered in the study. Importantly, high collinearity existed between C_{\max} and AUC . Several investigators have since suggested that the ratio of $\text{AUC}_{0-24}/\text{MIC}$ is more likely to be a “better” PD descriptor for aminoglycosides activity,^{29,89} in which an $\text{AUC}_{0-24}/\text{MIC}$ ratio of 80 to 160 has been advocated for its efficacy.^{89,90}

Although higher concentrations enhance aminoglycoside activity, prolonged exposure of such concentrations may lead to drug toxicity as well as the development of bacterial resistance. This type of resistance is known as adaptive resistance and is characterized by a slow, but reversible, concentration-independent killing.⁹¹⁻⁹³ Maximizing the C_{\max}/MIC ratio seems to reduce the development of adaptive resistance and the objective is likely achieved with extended daily dosing (EDD) as opposed to the traditional dosing schemes (i.e., twice or thrice daily dosing).⁹³ In a PD model designed to predict aminoglycosides activity against *A. baumannii* and *P. aeruginosa*, Tam et al further quantified the required C_{\max}/MIC ratio to prevent the resistance development.⁹⁴ In this study, a C_{\max}/MIC ratio of 20 for a once-daily amikacin dosing regimen and 30 for a 12-hour gentamicin dosing regimen was required for suppressing *A. baumannii* and *P. aeruginosa* regrowth, respectively. Based on these results, it could be inferred that the C_{\max}/MIC and $\text{AUC}_{0-24}/\text{MIC}$ ratios are the PD indices to consider for suppressing *A. baumannii* and *P. aeruginosa* resistant mutants, respectively.

Based on the available data, EDD rather than the traditional multiple daily dosing of aminoglycosides is currently advocated in an attempt to maximize their therapeutic potential and minimize resistance development. Furthermore, it has been shown in numerous clinical studies^{95,96} and several meta-analyses^{97,98} that the dosing recommendation is indeed appropriate and valid in reducing aminoglycosides toxicity and may increase the likelihood of successful treatment outcomes. Clinical data on these dosing effects on development of resistance remain sparse.

Beta-Lactams

The β -lactam antibiotics are made up of penicillins, cephalosporins, monobactams, and carbapenems. Because of their different spectrum and PD properties, carbapenems will be discussed separately in the following section. Beta-lactam antibiotics are generally hydrophilic in nature and display time-dependent kill characteristics. The percentage of $fT_{>\text{MIC}}$ ($\%fT_{>\text{MIC}}$) is regarded as the optimal PD index for their activity and, as such, maintaining effective drug exposure above the MIC should be the priority when this antibiotic class is used.³⁰ It has been generally suggested that the $\%fT_{>\text{MIC}}$ required for bactericidal effect is 50, 60 to 70, and 40% for penicillins, cephalosporins, and carbapenems, respectively.⁹⁹⁻¹⁰¹ In addition, relatively higher $fT_{>\text{MIC}}$ exposures are needed for maximal activity against the gram negatives as opposed to

the gram-positive pathogens. However, clinical data from critically ill patients have not consistently supported these targets. Some studies recommend these in vitro exposures to be the minimum antibiotic exposures required, with patients potentially benefiting from higher and longer antibiotic exposures than those previously described in in vitro and in vivo studies.^{33,102-106} It has also been demonstrated that maximal bactericidal activity occurs when drug concentrations are maintained at four to five times the MIC, with higher concentrations providing little added benefit.¹⁰⁶⁻¹⁰⁸ Therefore, it has been suggested that β -lactam concentrations should be maintained at least four to five times the MIC for extended periods during each dosing interval to ensure clinical success, particularly in severely ill patients.¹⁰⁹

It is still inconclusive whether the $fT_{>\text{MIC}}$ index predicts β -lactam resistance, although the potential link has been described in several in vitro⁴⁴ and in vivo experimental studies.^{62,110} Fantin et al utilized an in vivo animal model to suggest that the development of resistance against ceftazidime might arise should the drug concentration fall below the MIC for more than half of the dosing interval.¹¹⁰ The risk of developing resistance against a cephalosporin has also been linked to a low $\text{AUC}_{0-24}/\text{MIC}$ ratio.¹¹¹ This was further demonstrated by Stearne et al who found that an $\text{AUC}_{0-24}/\text{MIC}$ of 1,000 was required with ceftizoxime to prevent the emergence of resistant *Enterobacter cloacae* strains.⁴⁰ In another murine lung infection model, Goessens et al found that the growth of resistant *E. cloacae* strains was correlated with prolonged ceftazidime's $t\text{MSW}$.¹¹²

Based on the limited data on resistance suppression, β -lactams dosing that targets concentrations greater than four times the MIC for extended periods would be most appropriate.¹¹³ Importantly, research has shown that the objective can be obtained via frequent dosing or by utilizing extended infusion (EI) or continuous infusion (CI). However, the altered dosing schemes may potentially drive the emergence of resistance with suboptimal dosing, at least in theory, as these approaches tend to increase β -lactams $t\text{MSW}$. In a recent in vitro hollow-fiber infection model (HFIM) of *P. aeruginosa*, Felton et al suggested that EI of piperacillin/tazobactam was equivalent to intermittent bolus (IB) dosing in terms of the bactericidal effect and the prevention of resistance.¹⁴ However, the target concentration for the two approaches should be different in which the ratio of C_{\min}/MIC of 10.4 and 3.4 was required by EI and IB to suppress resistant mutants, respectively.

Carbapenems

In general, carbapenems have similar PK/PD characteristics when compared with other β -lactam antibiotics. Some studies have suggested that unlike other β -lactams, carbapenems possess a postantibiotic effect (PAE) against gram-negative bacilli, including *P. aeruginosa* strains,¹¹⁴ although this could not be confirmed in another study.¹¹⁵ This PAE property of carbapenems may explain a shorter $\%fT_{>\text{MIC}}$ for optimal bactericidal activity. Li et al further quantified the $\%fT_{>\text{MIC}}$ as $>54\%$ to achieve optimal microbiological outcome when meropenem is used in patients with lower respiratory tract

infections.¹⁰⁷ In addition, only a ratio of C_{\min}/MIC of >5 was significantly associated with clinical and microbiological cure in this cohort of patients. Further, Tam et al used an in vitro HFIM to demonstrate that a C_{\min}/MIC of >6.2 was required to suppress the development of resistant *P. aeruginosa* mutants.¹⁰⁸ The finding was later corroborated by the same group of investigators in a neutropenic mouse infection model, and in this current analysis, % $fT_{>MIC}$ of $>40\%$ was also associated with the selection of resistant mutants.¹¹⁶ Recently in an in vitro dynamic model simulating doripenem concentrations, Zinner et al found that resistant *P. aeruginosa* mutants were likely to be selected at drug concentrations that fell $\geq 45\%$ within the MSW ($\geq 45\%$ tMSW).¹¹⁷

Similar to the other β -lactam antibiotics, maintaining carbapenem concentrations at four to six times the MIC for extended periods is currently advocated to suppress the selection of resistant mutants. To achieve this objective, prolonging the duration of infusion is generally recommended when the antibiotic is used. However, EI instead of CI is the currently preferred dosing method when carbapenems are used considering the group's inherent drug instability in aqueous solutions. With increasing information and emerging data, clear distinction, in the context of stability problems, needs to be emphasized between the different members of the carbapenem group. While imipenem is indeed less stable, there are currently no practical reasons to oppose continuous meropenem infusion, as it has been successfully administered up to 8 hours (in a hospital environment) in numerous clinical studies without drug instability or degradation reports.^{118–120} In an in vitro HFIM examining cell-kill and resistance suppression for three *P. aeruginosa* strains, Louie et al demonstrated that a doripenem dosing regimen of 1 g infused over 4 hours was the solitary regimen that was able to completely suppress resistance for the full period of 10 days for wild-type isolates.¹²¹ Importantly, the investigators also reported that the dosing regimen produces concentrations at >6.2 times the MIC which were significantly associated with maximal resistance suppression in other evaluations.^{44,117} In addition, Chastre et al also observed lower occurrence of resistant *P. aeruginosa* strains arising in patients treated with EI of doripenem when compared with patients who received conventional imipenem dosing in a multicenter, randomized controlled trial of critically ill patients with ventilator-associated pneumonia.¹²²

Vancomycin

Vancomycin is a glycopeptide antibiotic and is a relatively hydrophilic drug. Some in vitro^{123,124} and in vivo animal studies¹²⁵ suggest that the bactericidal activity of the antibiotic is time dependent, whereas some have shown the ratio of C_{\max}/MIC to be equally important.¹²⁶ Recently, it has been generally accepted that achieving a high ratio of AUC_{0-24}/MIC would be more predictive of its clinical success. Studies by Moise-Broder et al were the earliest to quantify that a ratio of AUC_{0-24}/MIC of ≥ 400 is needed for an optimal bacteriological and clinical outcome when treating patients with *S. aureus* respiratory infections.^{35,127} The findings are consistent with the retrospective data evaluation of Zelenitsky et al and they

also described that higher exposures are needed, specifically a ratio of AUC_{0-24}/MIC of ≥ 578 , when treating critically ill patients with septic shock.¹²⁸ Owing to common clinical practice of measuring trough concentrations when vancomycin is used, a trough concentration ranging between 15 and 20 mg/L is recommended for optimal outcome in hospital-acquired pneumonia and complicated infections.^{129,130}

Although scarce data exist, it could be assumed that the development of resistance is linked to suboptimal vancomycin exposure. Through their in vitro PD model, Tsuji et al were able to conclude that the development of vancomycin-intermediate susceptible *S. aureus* (VISA) strains was driven by suboptimal vancomycin exposure in the setting of dysfunctional *agr* locus in *S. aureus*.¹³¹ In addition, the investigators also found that the AUC_{0-24}/MIC ratio needed to suppress resistance for the strains was fourfold higher than that in the parent strains. Charles et al observed that patients with VISA infections were more likely to present with low vancomycin trough concentrations (i.e., <10 mg/L).¹³² Based on similar findings to Charles et al's retrospective data evaluation,^{133,134} and considering the recommended trough concentrations for successful clinical outcomes in severe infections, vancomycin trough concentrations should also be maintained between ≥ 15 and 20 mg/L at all times to suppress resistance emergence.¹²⁹ Thus, loading doses of 25 to 30 mg/kg should be considered in critically ill patients to rapidly attain the target concentration and certainly, higher vancomycin doses of up to 40 mg/kg may be important to minimize resistance development. In addition, doses in excess of 5 g/daily were estimated to be necessary to achieve the target AUC_{0-24}/MIC ratio when treating VISA infections.¹³⁵ Increasing knowledge of the relationship between higher vancomycin exposures and drug toxicities may limit the dosing of this drug to limit the emergence of resistance.

Linezolid

Linezolid belongs to a class of antibiotics known as oxazolidinones, which was developed for the treatment of gram-positive infections. In a murine infection model, Andes et al demonstrated that optimal linezolid activity correlates well with the ratio of AUC_{0-24}/MIC , with a ratio of between 50 and 80 predicting the likelihood of successful treatment outcome.¹³⁶ However, higher clinical success rates may occur at AUC_{0-24}/MIC ratio of 80 to 120 for bacteremia, lower respiratory tract infections and skin structure infections as reported by Rayner et al.¹³⁷ Importantly, the investigators also showed that the drug exposure required for optimal treatment outcome was also dependent on the site and types of infection. In addition, the probability of treatment success appeared likely when linezolid concentrations were maintained above the MIC for the entire dosing interval. The finding corroborated two earlier rabbit endocarditis experimental models, which described linezolid as a time-dependent antibiotic where an $fT_{>MIC}$ of 40% is needed for optimal antibiotic activity.^{136,138} A 600-mg 12-hour dose is currently suggested to achieve these PD indices and hence, predicts successful treatment outcome. However, it is also imperative to emphasize that the antibiotic's PK is highly

variable,^{27,115,139–141} particularly in patients with severe infections, and the phenomenon has, in part, contributed to treatment failures as well as the increased occurrence of adverse events in such patients.^{137,142} As such, therapeutic drug monitoring (TDM) of linezolid is beneficial in this respect and emerging data are suggesting that general TDM may optimize patient outcomes when linezolid is used in critically ill patients. In the context of antibiotic resistance, low-dose linezolid (200 mg 12 hourly) has been associated with the development of *E. faecium* and *E. faecalis* resistant strains.¹⁴³ In addition, prior exposure and prolonged linezolid administration have been suggested to increase the likelihood of resistance development.^{144–146} Nevertheless, the development of resistance against the antibiotic has not been widely reported.^{147,148}

Daptomycin

Daptomycin is the first approved member of the cyclic lipopeptides with a potent activity against gram-positive pathogens including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci. In vivo experimental studies describe daptomycin to be a concentration-dependent antibiotic. The ratio of C_{max}/MIC in concert with AUC_{0-24}/MIC has been correlated with its efficacy in several in vivo animal studies.^{149–151} Safdar et al used a neutropenic murine thigh infection model to characterize the PD characteristics of the antibiotic.¹⁴⁹ In the infection model, the C_{max}/MIC and AUC_{0-24}/MIC ratio required for bacteriostasis ranged from 59 to 94 and 388 to 537 (total drug concentration), respectively. Similar ratios were required for bacteriostasis in two other clinical studies, which recruited healthy volunteers.^{152,153} Based on these suggested indices, optimal daptomycin exposure could be expected in most patients with modest dosing (4–6 mg/kg/d). However, the emergence of daptomycin-resistant strains has been reported with such dosing regimens^{154,155} and some experts recommend the use of higher dosing to curb this issue (i.e., 8–12 mg/kg/d),¹⁵⁶ which was shown to be safe in one retrospective data evaluation¹⁵⁷ and several case reports.^{158,159} A duration of therapy exceeding 2 weeks has also been documented to increase the likelihood of daptomycin resistance.¹⁵⁵

Fosfomycin

Fosfomycin, which was discovered more than 40 years ago but then forgotten, is a phosphonic acid derivative that possesses promising in vitro activity against carbapenem-resistant *K. pneumoniae*.¹⁶⁰ The introduction of fosfomycin into our current armamentarium of antibiotics was greeted with some skepticism due to major setbacks in its initial in vitro evaluation and this has, in part, contributed to its limited acceptance for clinical use. Although there are suggestions that fosfomycin's bacterial killing appears to be driven by $fT_{>MIC}$, the optimal PK/PD index relating to its activity remains to be established and requires further investigations.¹⁶¹ In addition, rapid bacterial killing was observed in several static-time kill studies when drug concentrations were maintained at two to eight times the MIC. Similar to the β -lactams, the development of fosfomycin

resistance is driven by low drug exposures and prolonged duration of antibiotic course.¹⁶² There has also been some debate concerning the rapid development of fosfomycin resistance when it is used as a monotherapy particularly in nonurinary tract infections. In a murine endocarditis model, Thauvin et al found that the combination of fosfomycin and pefloxacin was more effective in suppressing resistant *S. aureus* strains emergence when compared with fosfomycin alone.¹⁶³ In several in vitro and in vivo experimental studies, instances of synergism were also demonstrated against MRSA when fosfomycin was combined with the β -lactams,^{164,165} linezolid,¹⁶⁶ and moxifloxacin.¹⁶⁷ Combining fosfomycin with β -lactams is also strongly supported by in vitro data, which describe synergism between the two antibiotics against *P. aeruginosa* infections.^{168–170} However, whether the in vitro synergism would translate to increased clinical efficacy remains to be demonstrated. In a recent prospective study, fosfomycin, in combination with colistin, gentamicin, or piperacillin/tazobactam, provided promising bacteriological and clinical outcome data in the treatment of 11 critically ill patients with ICU-acquired infections caused by carbapenem-resistant *K. pneumoniae*.¹⁷¹ Based on limited clinical data in treating serious infections in the ICU and its high tendency for developing resistance, fosfomycin should not be used as a single agent and the choice of adjunctive antibiotic should be appropriately evaluated in future studies.

Colistin

Colistin is a polymyxin antibiotic, which is administered parenterally as colistin methanesulfonate (CMS). The antibiotic has concentration-dependent kill characteristics with a significant in vitro PAE against gram-negative pathogens.¹⁷² In vivo murine studies suggested that the most predictive PD index for its bacterial activity, particularly against *A. baumannii* and *P. aeruginosa*, is AUC_{0-24}/MIC .^{173,174} Based on observations in several lung infection models, the ratio of AUC_{0-24}/MIC between 50 and 65 has been suggested as the optimal PD target, although higher exposures were also described in thigh infection models.¹⁷⁵ The heteroresistance phenomenon, the situation whereby resistant subpopulations are present within a strain-considered susceptible based on MIC, is an emerging problem for the antibiotic and has been observed in clinical isolates of *A. baumannii*,^{176,177} *K. pneumoniae*,¹⁷⁸ and *P. aeruginosa*.¹⁷⁹ Further to this, rapid resistant mutants formation was demonstrated following colistin exposure in two recent in vitro PK/PD studies mimicking clinical dosing regimens in humans.^{180,181} This is particularly worrying as Garonzik et al suggested that the currently recommended CMS dosing regimen is suboptimal in a population PK analysis of 105 critically ill patients¹⁸² and their findings were corroborated by other investigators who recruited smaller number of patients.^{183,184} With increasing PK knowledge on the drug, Garonzik et al¹⁸² and Plachouras et al¹⁸⁴ further described optimized CMS dosing regimens in patients with varying degrees of renal function. The dosing proposed by Plachouras et al¹⁸⁴ has now been validated in a critical care setting by Dalfino et al in the

treatment of MDR infections.¹⁸⁵ Among the relevant recommendations concerning CMS dosing is the need for an initial loading dose, as the conversion of the prodrug CMS to the active entity of colistin is very slow and adequate colistin exposure may be delayed for a few days. Although theoretically plausible based on its PD characteristics, the adoption of EDD is not suitable on the basis of the resultant prolonged periods of low colistin concentrations leading to the formation of heteroresistance.^{173,174,180} Based on current PK data of critically ill patients^{182–184,186,187} and in vivo PK/PD experimental studies,^{173,174} colistin monotherapy would not be beneficial in maximizing therapeutic success and preventing resistance, particularly in patients with moderate-to-good renal function and for pathogens with MICs of ≥ 1 . In addition, a treatment course lasting more than 12 days has been found to be associated with the development of colistin resistance in two recent clinical studies.^{188,189}

Modifying Treatment Approaches to Prevent Emergence of Resistance

Combination Antibiotic Therapy

Although combining antibiotics is common during the treatment of infection, the relevance of the practice has been the matter of debate with conflicting conclusions. Proponents of combination therapy will strongly suggest that the approach will increase antibiotic exposure via extending coverage across a wider range of potential pathogens and, in some clinical evaluations, has been found to improve survival in severely ill patients.^{190–193} Further strong theoretical reasons to seriously consider a combination antibiotic approach include antibiotic synergism which enhances killing potency; combined activity against biofilm-growing pathogens; increasing tissue penetration; inhibition of pathogen's toxin and enzyme production; and prevention of resistance development. However, there is also clinical evidence indicating that combination therapy may not be superior, even harmful in some instances,^{194–196} as opposed to monotherapy in the treatment of gram-negative bacilli infections.^{197–199} Based on the current data, it could be deduced that combination antibiotic therapy may not benefit all patients but rather a select patient population with select infections. While monotherapy may be sufficient for most patients, critically ill patients with severe infections may benefit the most from rationally optimized combination therapy. Although some in vitro infection models^{200,201} and animal studies²⁰² clearly indicated benefits behind the approach, unfortunately, the vast majority of combination schemes were chosen randomly without considering the preclinical findings.²⁰³

In the context of resistance suppression, rationally optimized combination therapy may restrict the amplification of resistant mutants. Epstein et al²⁰⁴ suggest that the presence of more than two antibiotics at the infection loci (with drug concentrations above the MIC), each with a different killing mechanism, would “shut” the MSW and thereby suppress mutant growth.^{205–207} Apart from several preclinical stud-

ies,^{53,200,202,208,209} no randomized clinical trials to date have shown that the approach reduces the emergence of resistance. Furthermore, the benefit is particularly difficult to be demonstrated in clinical evaluations, which frequently recruit heterogeneous patient population and are not conducted long enough to detect the emergence of resistance. In the face of rapidly evolving resistance phenomenon, it is likely that we have to turn our attention to the concept of rationally optimized combination antibiotic therapy, particularly in the treatment of severely ill patients in the ICU. In addition, the approach is likely to be important early in the course of infection when the inoculum of the infecting pathogens is the highest.

Duration of Therapy

It has been increasingly shown in preclinical studies that prolonged antibiotic administration may play an important role in the formation of resistant mutants. Conversely, the longer antibiotic therapy persists, the more challenging it is to curtail the emergence of resistant pathogens. It has been suggested that an antibiotic regimen that lasts for only 4 to 5 days should be sufficient to produce maximal bactericidal effect with an added benefit of resistance suppression. Extending antibiotic exposure to more than 10 days is risky on the basis of resistance development whereby higher drug exposures are needed to suppress resistant mutants in this situation and if this threshold is not achieved, treatment failure ensues as the resistant population dominates. This phenomenon has been described by Tam et al in their in vitro model of *S. aureus* infection which investigated two garenoxin dosing regimens with different intensity, one with an AUC_{0–24}/MIC ratio of 280 and the other with 100.⁴² The investigators demonstrated that once the duration of garenoxin exposure increased beyond 5 days, the magnitude of dosing needed for suppressing resistant mutants also increased. The higher dosing regimen was found to suppress resistance amplification for 10 days, while the less intense regimen was only able to demonstrate the ability for 4 to 5 days.

At best, the common practice of administering an antibiotic for 10 to 14 days is currently based on limited data and expert opinion rather than it being an evidence-based approach. However, for some deep-seated infections such as osteomyelitis and endocarditis, prolonged antibiotic courses are essential. Instances of potential benefits from shortening the duration of antibiotic therapy in reducing the emergence of resistance while maintaining clinical efficacy have been increasingly described.^{210–213} Among these findings, Singh et al demonstrated that patients who received shortened antibiotic courses (i.e., ≤ 3 days) had reduced ICU stays, lower superinfection and resistance rates, as well as lower mortality rates compared with patients who received standard courses.²¹³ Further investigations are warranted to elucidate the exact duration of therapy that maximizes therapeutic outcome and suppresses resistance development. Until conclusive findings are made, antibiotic therapy should “hit hard” in the early course of infection and “stop early” to assist in resistance prevention.

Altered Dosing Approaches

Optimal and timely PK/PD target attainment has been associated with the likelihood of clinical success and resistance suppression in critically ill patients.⁶ However, organ function changes that may result from either infectious or noninfectious pathologic processes may alter antibiotics exposure. For example, the increase in V_d for hydrophilic antibiotics such as aminoglycosides,^{214,215} β -lactams,²¹⁶ glycopeptides,¹³⁵ and linezolid,²¹⁷ has been extensively documented in critically ill patients. Importantly, this phenomenon leads to suboptimal antibiotic concentration and may impair the attainment of desired PK/PD targets for optimal activity, particularly in the early phase of severe sepsis and septic shock. In this setting, higher initial loading doses of hydrophilic antibiotics should be applied to compensate for the volume expansion. In the context of resistance prevention, the approach may have the potential utility to rapidly reduce bacterial burden in the early stage of infection. Tsuji et al recently tested the impact of a front-loaded linezolid-dosing regimen on bacterial killing and resistance suppression in a HFIM of MRSA infection.²¹⁸ From a PD standpoint of bacterial eradication, their findings suggest potential benefits of increasing doses of linezolid early in therapy, although no differences were observed in terms of resistance suppression. Further preclinical studies are necessary to investigate this promising dosing strategy particularly in the context of resistance suppression, before it can be fully applied in clinical practice.

For the β -lactams, maintaining effective exposure for extended periods or increasing $\%fT_{>MIC}$ would be especially appropriate in the prevention of resistance particularly in critically ill patients. Research has shown that the traditional bolus dosing produces suboptimal antibiotic concentrations for much of the dosing interval, which may consequently favor resistant bacterial strains development.¹⁰⁹ Numerous preclinical and clinical PK/PD studies have demonstrated that improved β -lactams exposure could be achieved via EI or CI administration.²¹⁹ These altered dosing approaches may be especially important in patients who develop severe pathophysiological derangements and when less susceptible pathogens are present. However, more clinical studies are urgently needed to evaluate the relative ability of EI and CI versus IB dosing of β -lactam antibiotics in reducing the emergence of resistance if a global practice change is to be expected.

Conclusion

For decades now, clinicians have overused antibiotics and apparently did so with the notion that our continuous supply of new antibiotics would adequately address any emerging resistance concerns. That thought did not materialize and on the contrary, as our current antibiotic pipeline is nearly dry, infecting pathogens have tremendously outperformed our existing armamentarium thus far and they are becoming increasingly difficult to treat. The current situation that we are in is not surprising, as most of our treatment goals were previously focused on maximizing clinical and microbiological

cure and not on minimization of the emergence of antibiotic resistance. With numerous preclinical data indicating that the magnitude of the PK/PD indices for resistance suppression is generally higher than the thresholds required for clinical success, antibiotic dosing that only aims to optimize clinical efficacy may potentially amplify resistance formation by selecting mutant bacterial strains with reduced drug susceptibility. Furthermore, the relevance of commonly prescribed antibiotic dosing is questionable in severely ill patients as most dosing recommendations have been derived from studies that do not consider the occurrence of pathophysiological changes in critical illness. Therefore, with enhanced knowledge on antibiotic PK/PD over recent years, emerging data are suggesting that the PD-based dosing approach should not only aim to maximize clinical outcomes but also to include the suppression of resistance. In some antibiotics such as the quinolones, the PD thresholds needed to prevent the emergence of resistance is readily described but, unfortunately, is often neglected and not implemented in clinical practice, while for most antibiotic classes specific research is urgently needed. To curb the development of resistance, it is likely that we have to administer “the highest tolerated antibiotic dose” via alternative dosing strategies and should also consider the combined use of multiple antibiotics (that are rationally optimized), particularly early in the course of infection in severely ill patients.

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Conflict of Interest

None.

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